several unlabeled boxes which correspond to regions of Fig. 11.

The Applicants are again submitting substitute pages 10 and 11 that contain the corrections previously suggested by the Examiner. While considering the proposed amendments, the Examiner is respectfully requested to consider the relatively high level of knowledge and sophistication of one skilled in the retroviral vector arts. For example, a prototype retroviral vector is presented at the top of Figure 11A (MFG/Mo-LTR) that clearly and unambiguously marks the open box as the LTR sequence. Similarly, there can be no question that the shading corresponding to the ADA cDNA sequence is clearly labeled in Fig. 11(A)).

At page 10, lines 18-22, the specification teaches that the MPSV-LTR vector was constructed by inserting the 2694 bp *Ban* II-*Nhe* I fragment from the MFG vector. Accordingly, the two vectors are identical between the *Ban* II-*Nhe* I sites. Also, the Applicants respectfully submit that one skilled in the art would recognize that the shaded regions MPSV-LTR vector correspond to the Mo-LTR shown immediately above. Thus, there can be little question that the specification provides support for the MPSV-LTR shading. Further support for the shaded MPSV sequences may be found at page 10, lines 12-16 where the specification describes the 385 bp *Nhe I-Sac I* fragment containing the MPSV enhancer that is clearly marked in Fig. 11(A) (note: the "*Nhe I-Sac I*" fragment of MPSV DNA shown in the "MPSV-Enh" construct). Similarly, support for the shaded regions corresponding to Friend sequences are clearly and unambiguously shown in Fig. 11(A) and are

described in the specification at page 10, lines 22-25 (note: the "*Nhe I-Kpn I*" fragment (of Friend sequence from pFr-SV) that is clearly marked in Fig. 11(A).

In Paper No. 16, the Examiner had indicated that the requested amendment to the specification would not be entered because there is no specific support for the "...clear square, followed by a line, followed by diagonal square, black square, stippled square, followed by a line followed by a white square... [shown in the α-SGC vector of Fig. 11B]". In view of the Examiner's comments, the substitute page 10 does not attempt to incorporate revised boxes. The Applicants submit that one skilled in the art would not be confused by an error that is obviously typographical in nature. The Applicants further submit that the detailed description of α-SGC provided at Figure 4 (as well as indication of the specific restriction sites used to insert the recited sequences present at page 10, line 34 through page 11, line 3), provides guidance sufficient to remove any ambiguity caused by Figure 11B.

In view of the above comments, the amendments are not deemed to constitute new matter.

In view of the above corrections to the specification, the Examiner's previous rejection of claims 1-31 and 35-37 under 35 U.S.C. § 112, first paragraph is deemed to have been avoided by amendment.

II. Rejections based on prior art.

A. Rejections under 35 U.S.C. § 103 in view Cone and Mulligan in conjunction with Temin and Bender *et al*.

The Examiner had rejected Claims 1-4, 6-8, 20, 21, and 35-37 as obvious over the teaching of Temin in view of Bender *et al*. (Bender) and Cone and Mulligan (Cone). The key teaching in the above montage is apparently Cone's erroneous suggestion (no data were provided) that vector titers of greater than 10^5 enables the transduction of human cells without selective culture. To rebut Cone, Applicants submitted a Declaration by Dr. Lawrence Cohen as proof that Cone's unsupported and conclusory statement was wrong. The Examiner apparently dismissed Dr. Cohen's Declaration over the Jaffee paper's alleged lack of teaching of retroviral titers. The Applicants respectfully request that the Examiner consider that Dr. Cohen is an author of the Jaffee paper, and that paragraph 5 of Dr. Cohen's Declaration unambiguously states that results such as those reported in Jaffee (i.e., transduction without selection) require "...a <u>minimum</u> titer of approximately <u>$5x10^6$</u> transducing virus per ml...". In view of Dr. Cohen's clear statement of the <u>minimum concentration</u> of virus used by Jaffee, the Examiner's contention that "it is unclear whether the tenfold difference in titer stated by the Declaration to be the minimal effective titer in fact relates to the true differences in titer or is simply related to Jaffee's use of 10 mls and the Cone use of 1 ml of virus" is difficult to understand. Jaffee's use of ten mls of virus at a <u>minimum</u> concentration of <u>$5x10^6$</u> virus/ml effectively exposed $5x10^5$ cells to a total of $5x10^7$ virus. This represents a

minimum one hundred-fold net excess of transducing virus. Conversely, at best, Cone only taught the use of a mere two-fold excess of virus. The Applicants respectfully submit that one of ordinary skill in the art would recognize the substantial (fifty-fold) difference between the net virus-to-cell ratio suggested by Cone, and the minimum virus-to-cell ratio actually used by Jaffee to transduce cells without selection. Accordingly, the Applicants respectfully suggest that, given Dr. Cohen's Declaration and the teaching in the Jaffee reference, the method suggested by Cone could not have provided one of ordinary skill in the art with a reasonable expectation of successfully practicing the claimed invention. Accordingly, the Examiner is respectfully requested to withdraw the rejection of the pending claims as obvious under 35 U.S.C. § 103 over Cone.

CONCLUSION

In view of the foregoing amendments and remarks, the Applicants believe that the application is in good and proper condition for allowance. Early notification to that effect is earnestly solicited. If the Examiner feels that a telephone call would expedite the consideration of the application, the Examiner is invited to call the undersigned attorney at (415) 926-7405. The Commissioner is authorized to charge any underpayment or credit any overpayment to the deposit account number 16-1150 for any matter in connection with this response, including any fee for extension of time which may be required.

Respectfully submitted,

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